Dietary supplement-related adverse events reported to the California Poison Control System

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Purpose. Dietary supplement (DS)-related adverse events (AEs) reported to the California Poison Control System (CPCS) were studied.

Methods. The CPCS database was used to search for all telephone calls from consumers concerning DS-related AEs received during the six-month period between April and September 2002. The calls were characterized according to the substance involved, the caller's age (adult or pediatric), and the type of ingestion (accidental or intentional). Each exposure in which symptoms were reported was categorized as involving an AE. Each AE was assessed for severity and causality.

Results. Data on a total of 1183 telephone calls were retrieved, of which 828 calls (70%) met the study's inclusion criteria. DS exposure occurred in 389 adults (47%) and 438 children (53%). DS ingestion was accidental in 360 patients (43%) and intentional in 467 patients (56%). Exposure resulted in an AE in 480 patients (58%). AEs were reported in 353 patients (74%) who ingested products containing ephedra; other exposures frequently involved zinc, kava, creatine, and valerian. AEs were classified as moderate in 198 patients (41%) who ingested a DS and as severe in 40 patients (8%). One patient had a fatal reaction. Among the 480 AEs in DS-exposed consumers, the DS was classified as the definite cause of 1 AE (<1%) and a probable cause of 237 (49.4%). The most frequently reported AE symptoms were increased heart rate (45%), agitation (30%), vomiting (30%), and nausea (15%).

Conclusion. A majority of DS-related AEs reported by consumers to CPCS involved ephedra-containing products.

Index terms: Creatine; Dietary supplements; Dosage; Ephedra species; Kava; Minerals; Poisoning; Toxicity; Valerian; Zinc

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Dietary supplement (DS) sales totaled $17.7 billion in 2001, with herbal remedies contributing $4.2 billion to this amount.[1] A survey by *Prevention Magazine* in 2000 estimated that 100.4 million Americans were using vitamin and mineral supplements every day and that 37.2 million were using herbal products regularly.[2] The popularity of DS use may be ascribed to increased prescription medication prices, fear of adverse events (AEs) associated with prescription drugs, nonprescription availability of supplements, and perceptions that DS products are "natural" and therefore safer than prescription medications.

DS products are regulated by the Dietary Supplement Health and Education Act of 1994 (DSHEA).[3] Under DSHEA, DS labels may claim that the product improves general well-being, provides a benefit related to a classic nutrient deficiency, or affects the structure or function of the human body. Manufacturers cannot, however, make treatment or prevention claims. Labels can list warnings and contraindications, but this is primarily voluntary. Because product content and purity are not guaranteed and the manufacturing process is often not standardized, product efficacy and safety may vary significantly.

Although telephone calls to poison control centers regarding DS products increased from 6,914 in 1998 to 22,929 in 2002,[4] AEs related to these products often go unnoticed or unreported.[5] Supplement manufacturers are not required to report AEs involving their products to a third party, so these AEs are not rou-

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tinely communicated to consumers or health care professionals.[6] Health care professionals have been encouraged to report suspected or documented DS-related AEs to FDA's MedWatch program. However, in 2001 the Office of Inspector General reported that FDA received only 500 reports of such AEs, a number believed to represent less than 1% of all AEs caused by DS products.[7]

The California Poison Control System (CPCS), managed by the University of California San Francisco (UCSF) School of Pharmacy, is composed of four poison control centers in Sacramento, San Francisco, Fresno–Madera, and San Diego. Each site uses the same computer programs and databases, recording systems, and protocols and guidelines, such that similar care may be provided regardless of center location. In 1999, we studied DS-related AEs reported to CPCS between January 1997 and June 1998.[8] Data retrieval was limited by the lack of a universal coding system for this class of products. Specifically, each poison control center used individual coding terms, limiting the consistency and accuracy of our data. In March 2002, CPCS implemented a single coding system that allowed for more consistent retrieval of AE data.

The purpose of this study was to characterize AEs related to DS products reported to CPCS after implementation of the uniform coding system.

Methods

The study was approved by the human research committee at UCSF. The CPCS database was used to search for all telephone calls from consumers concerning DS-related AEs received during the six-month period between April and September 2002. Monthly reports of these calls were generated and analyzed by a single reviewer for study inclusion. All calls coded under the CPCS classification of DSs, herbals, and homeopathic products, which includes specific herbs, DS ingredients, amino acids, cultural medicines, and botanical and hormonal products, were reviewed. Calls involving exposure to a herbal product (single- or multiple-ingredient plant-derived products), a DS (single or multiple ingredients), vitamins, minerals, amino acids, cofactors, or enzymes were included in the analysis. Although γ-hydroxybutyrate (GHB) is not considered a herbal or DS, the CPCS classification identified it as such, and calls involving exposure to GHB were included in the study. Calls involving exposure to homeopathic remedies, topical products, traditional Chinese medicines, or non-DS products; calls involving animal-related exposures; and drug information calls were excluded. We excluded calls about traditional Chinese medicines because we were interested only in the Western use of commercially available herbs and supplements. We also excluded exposures involving whole plants (indoor or outdoor) that were clearly not used as a DS.

The telephone calls were characterized according to the substance involved, the caller's age (adult or pediatric), and the type of ingestion (accidental or intentional). Information recorded by the CPCS operator during the calls was reviewed to determine if an exposure had occurred and if related symptoms were reported. Each exposure in which symptoms were reported was categorized as involving an AE. Each AE was assessed for severity and causality using criteria adapted from other sources.[9-11] The severity of an AE was classified as lethal, severe, moderate, minor, or requiring no treatment.[9] A lethal AE was defined as one that directly or indirectly contributed to the patient's death. A severe AE was one that was potentially life-threatening, caused permanent damage, or required hospitalization. A moderate AE was one that resolved after an emergency room or physician office visit. A minor AE was one that required home treatment with fluid dilution or food. An AE was classified as requiring no treatment if no drug therapy, no discontinuation of the implicated substance, or no observation was required.

Causality of an AE was classified as definite, probable, possible, or doubtful.[10] An AE was classified as definite if the event followed administration of a DS, resolved when the DS was discontinued, and recurred upon rechallenge with the DS. Probable AEs were defined as those that followed administration of a DS, resolved when the DS was discontinued, and could not be explained by an existing clinical condition. A possible AE was an event that followed administration of the suspected DS but resolved despite continuation of the suspected DS or resolved when numerous DS products or drugs were simultaneously discontinued. An AE was classified as doubtful if there was no reasonable temporal relationship between the reaction and the DS. Concurrent medical conditions and concomitant medications were also considered as possible causes. The causality of AEs lacking sufficient information for causality to be assessed was categorized as unknown.

Results

Characteristics of telephone calls. Data on a total of 1183 telephone calls were retrieved, of which 828 calls (70%) met the study's inclusion criteria. Of the 355 telephone calls that were excluded from the analysis, most involved exposure to homeopathic remedies (n = 160); other non-DS products (n = 87), topical products (n = 52), plants (n = 27), or traditional Chinese medicines (n = 8). Twenty-one calls were excluded because the consumer called to request drug information rather than to report an AE. DS exposure occurred in 389 adults (47%) and 438 children (53%). Age was un-

known for 1 patient. DS ingestion was accidental in 360 patients (43%) and intentional in 467 patients (56%). Exposure resulted in an AE in 480 patients (58%) and no AE in 338 patients (41%); not enough information was available to characterize the exposure in 10 patients (10%). DS-related AEs were reported in 345 adults (72%) and in 134 children (28%). AEs following intentional ingestion were reported in 403 patients (84%), while AEs following accidental ingestion were reported in 76 patients (16%). For one exposure involving an AE, the type of ingestion was unknown.

Characteristics of products implicated in AEs. AEs were reported in 353 patients (74%) who ingested products containing ephedra. Of these patients, 332 (94%) ingested a multiple-ingredient ephedra product, and 21 (6%) ingested a single-ingredient ephedra product. AEs were reported in 111 patients who ingested DS products containing single ingredients (n = 83 [17%]) or multiple-ingredients (n = 28 [6%]) that did not include ephedra. For AEs reported in 16 patients (3%), the information reported to CPCS was insufficient for the product ingredients to be identified. AEs reported in patients exposed to nonephedra single-ingredient DS products are described in Table 1.

Severity and causality of AEs. Table 2 lists the severity of all AEs and those related to products containing and not containing ephedra. AEs were classified as moderate in 198 patients (41%) who ingested a DS, including 162 patients (46%) who ingested ephedra. Forty AEs (8%) were classified as severe, and one resulted in death. Twelve severe AEs and one lethal AE occurred in patients who ingested the DS in combination with other medications, illegal substances, or alcohol or in patients who attempted suicide by overdose.

Multiple- and single-ingredient products containing ephedra were involved in 26 (65%) of the severe AEs and the only death reported. The ephedra-containing multiple-ingredient products most frequently involved in severe reactions were Hydroxycut (Muscle Tech Research and Development Inc., Mississauga, Ontario, Canada) (n = 5), Metabolife (Metabolife Inc, San Diego, CA) (n = 5), Xenadrine (Cytodyne Technologies, Lakewood, NJ) (n = 3), Stacker 1 or 2 (NVE Pharmaceuticals, Andover, NJ) (n = 3), and Yellow Jackets (NVE Pharmaceuticals) (n = 2). Five of the severe AEs reported in patients who ingested ephedra-containing products also involved ingestion of other medications, illegal substances, or alcohol or overdose suicide attempts.

Single- and multiple-ingredient nonephedra products accounted for 12 (30%) and 2 (<1%) of exposures involving a severe AE, respectively. The most common single-ingredient products involved in these exposures contained kava (n = 3), GHB (n = 3), valerian (n = 3), creatine (n = 1), ginkgo (n = 1), and zinc (n = 1). The multiple-ingredient products involved in reports of severe AEs included Bloussant (Bloussant Product, Scottsdale, AZ), which contains saw palmetto, fennel seed, dong quai, damiana, blessed thistle, dandelion, watercress, black cohosh, wild yam, silicon dioxide, magnesium stearate, titanium dioxide, gelatin, and water and is used for breast enhancement, and Alluna (GlaxoSmithKline, Research Triangle Park, NC), which contains valerian root extract and hops extract and is used for sleep.

Among the 480 AEs involving ingestion of a DS, the DS was classified as the definite cause of 1 AE (<1%), a probable cause of 237 AEs (49.4%), a possible cause of 144 AEs (30%), and a doubtful cause of 30 AEs (6%). Causality was classified as unknown for 68 AEs (14.2%). Among the severe AEs, the causal relationship was classified as probable for 19 AEs (47.5%), possible for 12 AEs (30%), and doubtful for 7 AEs (17.5%).

AE outcomes. For exposures involving both single- and multiple-ingredient ephedra-containing products, increased heart rate was reported in 158 patients (45%), agitation with or without tremors in 105 (30%), vomiting in 105 (30%), and nausea in 52 (15%). Seizures were reported in 5 patients (1.5%) and were considered probably or possibly caused by ephedra in 3 patients and 1 patient, respectively. For 1 patient who had a seizure, causality was classified as unknown. Among the 26 severe AEs reported in patients who ingested ephedra, increased heart rate was reported in 15 patients (58%), electroencephalographic changes in 5 (19%), vomiting in 5 (19%), agitation in 5 (19%), hypertension in 5 (19%), seizures in 2 (8%), and myocardial infarction in 1 (4%).

The lethal exposure occurred in a 34-year-old woman with a repeated history of alcohol and substance abuse who ingested a multiple-ingredient product. The woman collapsed while talking on the telephone and had no pulse when she was delivered to the hospital. She was resuscitated over a 45-minute period and received electric cardioversion seven times. She had a pulse rate of 135 beats/min, a blood pressure of 106/50 mm Hg, and a respiration rate of 16 breaths/min. Oxygen saturation was 75%, and blood-gas pH was 7.22. Blood chemistry and complete blood count results were normal. The patient was comatose and required intubation and mechanical ventilation in the intensive care unit. Follow-up by CPCS found that the patient had no cerebral function and no reflexes. She was diagnosed as having had an overdose on the product (Xenadrine) that produced anoxic injury. The patient died two days after the ingestion.

Table 1 characterizes outcomes of AEs caused by single-ingredient nonephedra products for which more than three AEs were reported. Additional severe AEs have been reported

Table 1.
Single-Ingredient Nonephedra Dietary Supplements Associated with Three or More Adverse Events (AEs)[a]

Dietary Supplement	Total No. (%[b]) AEs	Symptoms or Signs (No. Cases)	
		AE Mild or Moderate or No Treatment Required	AE Severe
Zinc[c]	12 (2.5)	Nausea (8), vomiting (4)	Severe GI distress after suicide attempt with opiates, zinc, and folic acid (1)
Creatine	5 (1)	Proteinuria (1), agitation (3), vomiting (2)	SCr conc. of 5.3 mg/dL after taking creatine 5 mg/day for several months, urinanalysis positive for THC and opiates, SCr conc. decreased to 1.8 mg/dL after discontinuation of creatine (1)
Kava	12 (2.5)	Headache (3), drowsiness (4), dyspnea (1), nausea (1), pruritus (1)	Fatigue, drowsiness, vomiting (2); respiratory depression after ingestion of kava and alcohol in possible suicide attempt (1)
Valerian	12 (2.5)	Vomiting (1), drowsiness (4), agitation (4), nausea (1)	Probable anaphylactic reaction (hives and respiratory distress) (1); drowsiness and vomiting (1); myosis, tremor, and coma following suicide attempt with valerian, acetaminophen, diphenhydramine, ibuprofen, and aspirin–caffeine combination product (1)
Echinacea	6 (1.3)	Rash (2), headache (1), drowsiness (2), hallucinations after ingestion of echinacea with lorazepam and pantoprazole (1)	NA
St. John's wort	6 (1.3)	Diarrhea (3), vomiting (2), drowsiness (1), agitation (2), rash (1)	NA
Saw palmetto	5 (1)	Pruritus (2), tingling of extremities (1), dizziness (1), nausea (2), vomiting (2)	NA

[a]GI = gastrointestinal, SCr = serum creatinine, THC = tetrahydrocannabinol, NA = not applicable.
[b]Percentage of all AEs reported to the California Poison Control System (n = 480).
[c]Products containing zinc gluconate (n = 4), zinc amino acid chelate (n = 1), zinc sulfate (n = 1), or an unspecified salt of zinc (n = 6).

Table 2.
Severity of Adverse Events (AEs)

Severity	No. (%) AEs		
	All	Involving Ephedra	Not Involving Ephedra
No treatment required	80 (16.7)	55 (15.5)	26 (23.4)
Minor	75 (15.6)	49 (13.9)	23 (20.7)
Moderate	198 (41.3)	162 (45.9)	28 (25.5)
Severe	40 (8.3)	26 (7.4)	14 (12.6)
Lethal	1 (0.2)	1 (0.3)	0 (0)
Unknown	86 (17.9)	60 (17)	20 (18.0)
Total	480 (100)	353 (100)	111 (100)[a]

[a]Sixteen AEs were not classified by product involved.

to CPCS. A woman attempted suicide by swallowing 20 tablets of Unisom (Pfizer Inc, Morris Plains, NJ), which contains doxylamine, and 12 tablets of Bloussant. The patient arrived at the emergency department with drowsiness and tachycardia and was later admitted to the hospital for precautions against seizures and for cardiac monitoring.

A suicide attempt was reported in one patient who ingested Alluna. The patient was admitted to the hospital after having a seizure at home. She had been taking Alluna in combination with bupropion, paroxetine, marijuana, and methamphetamines.

The one severe AE involving ginkgo was a multiple-ingestion case in which the patient had taken ginkgo but was also receiving amitriptyline hydrochloride and an acetaminophen–hydrocodone combination product. The patient was admitted to the hospital with new-onset seizure activity. Information regarding the dosage and duration of ginkgo use was not provided in the report.

Three severe AEs involved GHB. All three patients took the product together with amphetamines. These patients were in their 20s and were admitted to the hospital with hallucinations, paranoia, confusion, agitation, or tachycardia or a combination thereof. Intravenous benzodiazepines with or without phenobarbital were necessary to resolve the symptoms.

Discussion

Characteristics of telephone calls. Using the new classification system for DS-related AEs developed by CPCS in 2002, we identified 828 DS exposures and 480 AEs over six months. This contrasts dramatically with our earlier study, in which we

were able to identify only 599 DS exposures and 233 AEs over an 18-month period when the new classification system was not in place.[8] It appears that the new coding system was better able to identify AEs involving DS products. The increased reporting to CPCS appears to be consistent with the increased reporting observed nationally. It is also possible that consumers were reporting AEs to CPCS more frequently or that the use of these products had increased, resulting in a larger volume of telephone calls.

The overall frequency of exposure to DS products was similar between adults and children; however, exposure associated with AEs was more common in adults (72%). AEs were more likely to be reported after intentional ingestion (84%). This is not surprising, since it is logical that adults would be much more likely to intentionally ingest a product, and children would be more likely to be victims of accidental ingestion. Most of the intentional ingestions in children occurred when parents gave DS products to their children.

Characteristics of products implicated in AEs. At the time of our study, ephedra was widely available for weight loss. Therefore, it is not surprising that 73.5% of exposures in which an AE was reported involved ephedra-containing products marketed for appetite suppression, weight loss, or increased energy. Our results are consistent with data from the American Association of Poison Control Centers (AAPCC) showing that ephedra-containing products accounted for 64% of all AEs in 2001.[11] In 2004, FDA published a final rule prohibiting the sale of DS products containing ephedrine alkaloids (ephedra), which should drastically reduce the number of DS-related AE reports to poison control centers.[12]

Zinc, kava, and valerian were identified as the nonephedra products most frequently involved in AEs. Products containing these ingredients consistently rate among the top-selling DS products.[13,14] Zinc preparations are commonly used to relieve symptoms of the common cold, while kava and valerian have sedative–hypnotic properties and are used for anxiety and insomnia, respectively.

AE severity and causality. Nearly 50% of the AEs were classified as moderate to severe. In 30% of patients, DS products associated with severe AEs were used in combination with other medications, illegal substances, or alcohol. This occurred more frequently with nonephedra products than with ephedra-containing products. As such, the DS may have been inadvertently involved in the AE but may not have been the primary cause. In addition, six severe AEs (five involving nonephedra products and one an ephedra-containing product) and the lethal AE occurred in patients who were reportedly trying to commit suicide.

DS products involved in severe AEs were more likely to contain ephedra and to be multiple-ingredient preparations. Bent et al.,[11] using AAPCC data, also concluded that the relative risk of AEs for ephedra-containing products was 10–40 times greater than the risk for other herbal products.

GHB, kava, and valerian were the nonephedra products most commonly associated with severe AEs. GHB is an illegal substance, and its sale is prohibited. Among younger adults, GHB is commonly used as a recreational drug.[15] The severe AEs reported in patients who ingested kava involved one suicide attempt, an unintentional ingestion by a two-year-old child, and sedation in one adult. The severe AEs reported in patients who ingested valerian included one suicide attempt, an anaphylactic reaction in an adult, and sedation in an adult. Except for the anaphylactic reaction, the reported symptoms were consistent with the pharmacologic properties of both herbs.[16]

Almost half (49.2%) of AEs (for both nonephedra and ephedra-containing products) were classified as probably caused by DS products, and causality was classified as possible for almost a third (30%). Our assessments of causality were limited by the amount of information provided for each patient. Causality could not be definitely determined in cases of combination-product or multiple-product ingestion or lack of ingredient information.

AE outcomes. AEs involving ephedra-containing products were similar to those that have been reported elsewhere in the literature, such as tachycardia, hypertension, vomiting, agitation, and seizures.[17] Several investigators have reported on the safety of ephedra use.[18,19] Haller and Benowitz[17] reported hypertension as being the most frequent AE, in addition to tachycardia, palpitations, stroke, seizures, and death. Morgenstern et al.[19] found that high doses of ephedra (>32 mg/day) were associated with an increased risk of hemorrhagic stroke.

Reports of ephedra-related ADEs prompted the U.S. Department of Health and Human Services to actively investigate the risks posed by ephedra-containing DS products. A study by the RAND Corporation commissioned by the National Institutes of Health reviewed the safety and efficacy of ephedra-containing products for weight loss and increased physical performance.[18] The authors concluded that, compared with placebo, ephedra-containing products were associated with a two to three times greater risk of nausea, vomiting, central-nervous-system symptoms (such as anxiety and mood changes), autonomic hyperactivity, and palpitations.

The AEs most often associated with nonephedra DS products were nausea and vomiting (zinc products), sedative–hypnotic reactions

(kava and valerian), and proteinuria and elevated serum creatinine (creatine). These reactions have been documented previously and, in the case of kava, valerian, and creatine, are consistent with their pharmacologic properties.[16,20,21] Ginkgo was associated with one severe AE resulting in a seizure. Although seizures have been previously reported with ginkgo, this reaction is more likely to occur with product contamination by ginkgo seeds, which contain a neurotoxin.[22] The patient described in our study, however, also ingested amitriptyline, a medication that lowers the seizure threshold.

Severe AEs involving GHB occurred in patients with symptoms of withdrawal (e.g., vomiting, dizziness, tremor, seizures). The withdrawal symptoms were consistent with previous reports.[15]

Limitations. Underreporting of AEs may have limited our findings; AE underreporting has been observed among consumers using prescription and nonprescription medications.[23] Most DS manufacturers do not provide a telephone number for reporting AEs on their package labeling. When a number is provided, it is usually that of the manufacturer, who is not required to inform FDA or local poison control centers of these incidents. (One way to increase AE reporting might be to include the telephone number for FDA's MedWatch program or the local poison control center on the labeling of these products.)

Underreporting of AEs may also have been related to the severity of the symptoms. Persons with more severe symptoms may have been less likely to call a poison control center and more likely to contact emergency medical services, and persons with milder symptoms may have been more likely to contact a poison control center.

Some 30% of telephone calls were excluded from analysis because the consumer was using CPCS as a source of drug information rather than to report a possible AE. Consumers may be unaware that poison control centers are designed to manage undesirable exposures, toxicity, and overdoses rather than to provide drug information.

Another study limitation is the unknown accuracy of the causality assessments. It is difficult to determine with certainty that a particular ingredient caused an AE without proper chemical analysis to rule out adulteration or plant misidentification.[24] Also, some calls involved coingestion of a DS with a prescription drug, alcohol, or a drug of abuse, making inferences regarding causality or clinical effect questionable.

The analysis was contingent on information recorded by CPCS operators. It is possible that certain calls were miscategorized. Lack of follow-up by CPCS operators for some calls, in addition to lack of patient follow-up through emergency room visits or physician office appointments, contributed to the unknown outcomes of some of the calls.

Only six months' worth of data were analyzed. A longer study period might have provided greater insight into AEs associated with DS products.

Conclusion

A majority of DS-related AEs reported by consumers to CPCS involved ephedra-containing products. Other exposures frequently involved zinc, kava, creatine, and valerian.

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Medicare-approved drug discount cards and prescription drug prices

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Purpose. Prescription drug prices with and without the use of Medicare-approved drug discount card programs (MADDCs) to purchase medications were studied.
Methods. The Medicare.gov Web site was used to determine if the 200 most frequently prescribed drugs in the United States in 2003 were covered by a MADDC. The lowest and highest MADDC prices at local and mail-order pharmacies and the corresponding non-MADDC prices at the same community pharmacies or an Internet pharmacy, respectively, were determined. Wilcoxon signed rank tests were used to determine if there was a difference between non-MADDC medication prices and MADDC prices.
Results. Of the top 200 medications prescribed in 2003, 192 (96%) and 189 (94.5%) were covered by at least one MADDC in a local pharmacy or mail-order pharmacy, respectively. Overall, MADDCs saved money compared with purchasing medications without a MADDC ($p < 0.001$). However, a MADDC resulted in a higher price than the retail non-MADDC price for 61 (31.8%) of the prescription medications at local pharmacies, and using a MADDC at a mail-order pharmacy resulted in a higher price than the Internet pharmacy non-MADDC price for 143 (75.7%) of the drugs.
Conclusion. MADDC prices for common prescription medications were generally lower than prices when MADDCs were not used. The highest mail-order MADDC prices were often higher than Internet non-MADDC prices.

Index terms: Cards; Costs; Health-benefit programs; Pharmacy; Prescriptions; Pricing
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Many Americans lack adequate prescription drug insurance, and access to prescription drugs is a growing concern because of increasing prescription drug costs.[1] In 2001, $140.8 billion was spent on prescription drugs by both public consumers ($109.4 billion) and private consumers ($31.4 billion).[2-5] This sum represents a greater than threefold increase since 1990, when $40.3 billion was spent.[2-5] In 2002 and 2003, the amount spent on prescription drugs by consumers jumped to $161.8 billion and $179.2 billion, respectively.[4] By 2012, spending is projected to increase to $445 billion or more.[3,6]

Inadequate prescription drug coverage can lead to financial devastation for individuals. In 2001, 1 in 10 Americans surveyed by the Kaiser Family Foundation and the Harvard School of Public Health spent $1000 or more out-of-pocket on prescription drugs.[7] By 2010, greater than 15% (an increase from the 9% reported in 1999) of Americans' annual expenditure on personal health care will be spent on prescription drugs. Personal health care is defined as therapeutic goods or services that are rendered to treat or prevent a specific disease or condition in a spe-

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